The impact of diabetes on cognitive impairment and its progression to dementia:

A population-based cohort study

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by

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Tiivistelmä – Referat – Abstract

Background: Despite the well-established link between diabetes and dementia risk, the impact of prediabetes and diabetes on the prodromal dementia phase remains controversial. In this study, we investigated whether prediabetes and diabetes increase the risk of cognitive impairment–no dementia (CIND) and accelerate its progression to dementia, as well as the possible underlying mechanisms.

Methods: In the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), one cohort of cognitively-intact individuals (n=1,837) and one cohort of individuals with CIND (n=671) aged ≥60 years were followed for up to 15 years. At baseline and each follow-up (every 3 or 6 years), a neuropsychological test battery was administered, and the domains of episodic memory, processing speed, executive function, visuospatial abilities, and language were derived. CIND was defined as having no dementia and cognitive performance ≤1.5 SDs below age group-specific means in at least one cognitive domain. Dementia was diagnosed according to DSM-IV criteria. Diabetes (controlled and poorly-controlled) was diagnosed by physicians through medical assessment, clinical records, and glycated hemoglobin (HbA1c) ≥6.5%. Prediabetes was identified as HbA1c 5.7-6.4% in diabetes-free participants. Clinicians diagnosed heart disease and collected blood samples used to measure C-reactive protein (CRP). Data were analyzed with Cox regression models adjusted for possible confounders.

Results: At baseline, in the cognitively-intact cohort, 133 (7%) participants had diabetes and 615 (34%) had prediabetes. During follow-up (mean 9.2 ± 3.0 years [range=2.2-15.5 years]), 544 (30%) individuals in the cognitively-intact cohort developed CIND. Poorly-controlled diabetes (HbA1c ≥7.5%) was associated with 2-times higher risk of CIND (HR 2.0, 95% CI:1.11-3.48) than diabetes-free participants.

In the CIND cohort, 84 (13%) had diabetes and 238 (36%) prediabetes. During follow-up (mean 7.7 ± 4.0 years [range=0.2-15.2 years]), 132 (20%) individuals progressed to dementia. Poorly-controlled diabetes was associated with 3-times higher risk of dementia progression (HR 3.3, 95% CI: 1.29-8.33). Furthermore, comorbid heart disease and diabetes was associated with 2.5-times higher risk of progression to dementia (HR 2.5, 95% CI: 1.17-5.47), particularly if the diabetes was poorly-controlled (HR 5.8, 95% CI: 1.72-19.3). Similarly, having elevated CRP levels and diabetes was associated with increased risk of progression to dementia (HR 4.1, 95% CI: 1.15-14.2), especially in participants with poorly-controlled diabetes (HR 13.6, 95% CI: 1.89-98).

No associations between prediabetes and CIND were detected in either cohort.

Conclusions: Diabetes, especially if poorly-controlled, increases the risk of cognitive impairment and accelerates its progression to dementia. The diabetes-associated progression from CIND to dementia is further exacerbated by the presence of heart disease and elevated levels of systemic inflammation.

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Diabetes, dementia, cognitive impairment, vascular disorders, inflammation

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Abbreviations

ADA – American Diabetes Association
AGEs – advanced glycation end products
ANOVA – analysis of variance
APOE ε4 – apolipoprotein ε4 allele
BMI – body mass index
CI – confidence interval
CIND – cognitive impairment-no dementia
CRP – C-reactive protein
DLB – dementia with Lewy bodies
DSM-IV – *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition
FINGER – Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FPG – fasting plasma glucose
FTLD – fronto-temporal lobar degeneration
HbA1c – glycated hemoglobin
HR – Hazard Ratio
IADL – instrumental activities of daily living
ICD-10 – International Classification of Disease, 10th revision
IDF – International Diabetes Federation
IGT – impaired glucose tolerance
IL-6 – interleukin 6
IR – incidence rate
MCI, mild cognitive impairment
MI – myocardial infarction
mmHg – millimeters of mercury
OGTT – oral glucose tolerance test
OR – Odds Ratio
RCT – randomized controlled trial
RERI – relative excess risk due to interaction
SD – standard deviation
SNAC-K – Swedish National Study on Aging and Care-Kungsholmen
WHO – World Health Organization

Introduction

I. Diabetes

Type 2 diabetes (hereafter, diabetes) is a chronic, progressive disorder characterized by persistently elevated levels of glucose in the blood (i.e. hyperglycemia).[1] Diabetes is a highly multifactorial disease, and hyperglycemia can arise from one or several mechanisms: (i) reduced insulin secretion from pancreatic beta cells, (ii) increased glucagon secretion from pancreatic alpha cells, (iii) increased glucose production in the liver, (iv) increased lipolysis, (v) increased glucose reabsorption in the kidneys, (vi) reduced incretin effect in the small intestine, (vii) impaired glucose uptake in skeletal muscle, liver, and fat, and (viii) neurotransmitter dysfunction and brain insulin resistance.[2]

An individual's risk of developing diabetes is attributed roughly equally to environmental exposures (e.g. physical inactivity, excess food intake, poor nutritional quality) and genetics.[3] Advanced age is another major risk factor for diabetes.[1,4]

Prevalence and cost of diabetes

An estimated 425 million people worldwide live with diabetes, including 58 million in Europe and 500 thousand in Sweden.[4] Overall diabetes affects 8.8% of the global adult (20-79 years) population and 9.6% of the global population over the age of 65.[4] Since diabetes is asymptomatic in the early stages, approximately half of all diabetes cases are undiagnosed and therefore untreated.[4]

Due to the aging global population – combined with shifting eating patterns and a rise of occupational and leisure activities that promote a primarily sedentary lifestyle – the burden of diabetes and dementia is poised to dramatically increase in the coming decades.[4] According to the International Diabetes Federation (IDF) 2017 Atlas, global diabetes prevalence is projected to grow 48% to 629 million by 2045.[4] This translates to a steep financial costs to healthcare systems alongside the obvious human costs. The global economic burden of diabetes has been estimated at $1.3 trillion annually and is projected to surpass $2.5 trillion by 2030.[5]

Prediabetes

A major challenge in addressing the global burden of diabetes is a growing epidemic of prediabetes, a state of intermediate hyperglycemia situated between normal glycemia and diabetes.[6] Prediabetes affects approximately 352 million people worldwide (7.3% of the global adult population) and this is expected to increase to 587 million people (8.3% of the global adult population) by 2045.[4] Prediabetes is especially common in older adults, affecting 52% of European adults (and 53% of Swedish adults) aged ≥60 years, according to IDF.[7]

Prediabetes is a high-risk state for developing overt diabetes.[6] It has been estimated that between 5% and 10% of the prediabetes population progresses to diabetes annually and 70% of all prediabetes

cases ultimately will give rise to diabetes.[6] Approximately 90% of prediabetes cases are undiagnosed, owing to heterogeneity in the diagnostic criteria for prediabetes, a lack of prediabetes screening efforts, and low awareness of prediabetes as a serious health condition.[8,9]

However, in contrast to diabetes, prediabetes is not a chronic condition. Not everyone with prediabetes will progress to diabetes, and it is even possible to revert to normoglycemia. Indeed, a recent longitudinal study estimated that 22% of people with prediabetes could revert back to normoglycemia over more than a decade of follow up.[10] This makes prediabetes an ideal window for interventions to prevent diabetes and its complications.

Diabetes complications and comorbidities

Chronic hyperglycemia has detrimental effects on many organ systems of the body. Accordingly, diabetes is associated with a wide range of adverse complications including cardiovascular disease, kidney disease, retinopathy, neuropathy, and low-extremity amputations, making it a leading cause of death and disability worldwide.[1,4] The American Diabetes Association (ADA) recommends a glycated hemoglobin (HbA1c) target of <7% to prevent or delay the onset of these complications, particularly microvascular complications (i.e. kidney disease, retinopathy, and neuropathy).[11] However, a less strict glycemic target of HbA1c <7.5% is considered more appropriate for older adults to minimize their risk of hypoglycemia (i.e. dangerously low blood sugar) and to reduce therapeutic complexity.[12] Furthermore, in patients with a shorter life expectancy, there are diminishing benefits to the strategy of using strict glycemic control to lower the risk of long-term diabetes complications.[13]

Heart disease (e.g. myocardial infarction [MI], coronary artery disease, heart failure) is one of the major comorbidities of diabetes, and it is associated with increased mortality.[14,15] It has been estimated that over half of people with diabetes (67% of men and 57% of women) will eventually develop heart disease,[14] and as high as 80% could ultimately die from cardiovascular causes (vs. 30% of the diabetes-free population).[15] The mechanisms behind the association between diabetes and heart disease are complex and multifactorial. The hyperglycemia that characterizes diabetes can damage blood vessels, contributing to the risk of ischemic stroke and MI.[16] At the same time, people with diabetes are more likely to have existing risk factors for atherosclerotic heart disease, such as hypertension, high cholesterol, and obesity.[17]

II. Dementia

Diabetes affects also the brain.[18] To this end, dementia and cognitive impairment are becoming increasingly recognized as potential complications of diabetes.

Dementia is a highly heterogeneous syndrome characterized by progressive loss of cognitive functioning and physical independence. Cognitive dysfunction can manifest as memory loss,

challenges in planning and problem solving, confusion with time and place, problems with speaking or writing, impaired judgment and decision making, and behavioral symptoms such as changes in mood and personality.[19] Beyond the cognitive symptoms, dementia also involves loss of functional independence for instrumental activities of daily life (IADL; e.g. eating, bathing, dressing, personal hygiene, toilet hygiene, moving from one place to another).[19] This translates to an enormous physical and psychological burden for patients, their families, and society – made worse by the current lack of disease-modifying therapy for dementia.[20]

The majority (50% to 70%) of dementia cases are caused by Alzheimer's disease, characterized by neuronal death and damage accompanied by abnormal accumulation of the protein beta-amyloid outside neurons and the protein tau inside neurons.[19,21] The next most common cause of dementia is vascular dementia, which involves neuronal damage from infarcts or bleeding in the brain due to blood vessel blockage.[19,21] Other neurodegenerative forms of dementia include dementia with Lewy bodies (DLB) and frontotemporal lobar degeneration (FTLD).[19] Furthermore, it is increasingly recognized that neurodegenerative and vascular pathologies often co-occur in the aging brain, making mixed pathologies the most common cause of dementia.[22,23]

Prevalence and cost of dementia

An estimated 50 million people worldwide live with dementia, including approximately 10.5 million in Europe.[19,24] Likewise, approximately 10 million new cases of dementia are diagnosed worldwide each year.[25] Prevalence increases dramatically with age: in the European population, dementia prevalence starts at 2.6% for individuals aged 65-69 and rises to 4.3% for ages 70-74, 7.4% for ages 75-79, 12.9% for ages 80-84, 21.7% for ages 85-89, and 43% for ages ≥90.[26] As the global population ages, the World Health Organization (WHO) predicts that dementia prevalence is on pace to triple to 150 million by 2050.[25] In financial terms, dementia accounts for between $818 billion and $948 billion in global spending per year, costs that are rising at an alarming rate of >20% year over year.[21,27] Per patient, dementia is the most costly disease facing society.[21,28]

Cognitive impairment

Dementia is characterized by a long preclinical and prodromal phase.[29] Brain changes associated with dementia could occur 20 years or more before any clinical symptoms begin to manifest.[19] Likewise, studies indicate that subtle, early impairments in various cognitive abilities (namely domains such as memory, attention, information processing speed, executive function, reasoning, visuospatial abilities, and language)[21,30] can be detected nearly a decade before the clinical diagnosis of dementia.[31,32]

Cognitive impairment represents an intermediate state between expected age-related cognitive changes and the appearance of dementia.[33] Over the years, the concept of cognitive impairment has evolved and several terminologies and relative operationalizations have been proposed. Mild cognitive impairment (MCI) is the most common construct within this.[33] While ongoing refinements

of the definition are still debated,[33,34] in general MCI is agreed to involve the following: (i) absence of dementia; (ii) subjective cognitive complaint; (iii) objective impairment in one or more cognitive domains (memory, executive function/attention, language, or visuospatial skills); and (iv) essentially preserved independence in functional abilities (IADL).[35] A similar but more broadly-defined formulation for cognitive impairment is cognitive impairment–no dementia (CIND), which describes a level of cognitive functioning that falls below normal, but does not meet the criteria for dementia.[36,37] MCI is well-suited for making diagnoses in clinical practice since its criterion of subjective cognitive complaint is associated with increased risk of progression to Alzheimer's dementia.[38,39] For epidemiological purposes, CIND appears better suited as its strength lies in capturing a broader spectrum of cognitive impairment, including forms attributable to non-degenerative causes (e.g. related to vascular or metabolic conditions).[38]

Systematic reviews estimate that 16% to 20% of people ≥65 years have MCI globally,[38] and between 32% and 38% of MCI cases progress to dementia within five years.[39,40] Though CIND has been less addressed, its estimated prevalence falls within a similar range: 25% in a study of Swedish twins (≥65 years),[41] 16.8% in a Canadian population study (≥65 years),[36] and 12.8% in a Portuguese population study (55-79 years).[42] Reported progression rates from CIND to dementia have been estimated at 12% to 38% over one year,[43,44] 36% over two years,[45] and 42% over five years.[46]

While on one hand the high prevalence of cognitive impairment foreshadows a rise in dementia incidence, on the other hand emerging evidence suggests that up to 22% of people with cognitive impairment could eventually revert to nearly normal cognitive function.[47,48] Therefore, similarly to prediabetes, cognitive impairment also represents a hopeful window for intervention and risk factor control to prevent the onset of overt dementia.

Risk factors for dementia

Advanced age is by far the dominant risk factor for cognitive impairment and dementia, followed by a positive family history of dementia and, for Alzheimer's disease specifically, carrying one or more copies of the apolipoprotein ε4 (APOE ε4) allele.[19] However, recent estimates suggest that over half of the burden of dementia worldwide could be attributable to seven potentially modifiable risk factors.[49] These include diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment.[49] Specifically, diabetes confers nearly double the risk of dementia,[18,50] and it has been estimated that nearly 3% of all dementia cases are attributable to diabetes itself[51] and as much as 10% are attributable to the spectrum of metabolic disturbances brought on by diabetes.[18]

III. Diabetes and Cognitive Impairment

Despite the body of evidence associating diabetes with dementia, it is less clear whether there is a relationship between diabetes and cognitive impairment – cross-sectionally, longitudinally, and in terms of progression from cognitive impairment to dementia.

Cross-sectional relationship

In the past decade, eight studies have addressed the relationship between diabetes and cognitive impairment. The methods and findings of these studies are summarized in **Appendix 1**. Overall, five studies reported a positive association between diabetes and cognitive impairment,[52–56] while two reported no association.[57,58] The remaining study partitioned the analysis by age, finding an association between diabetes and cognitive impairment in middle age (50-65 years) but not old age (65-80 years).[59] Altogether these findings suggest that diabetes is likely associated with cognitive impairment, but results are mixed.

Discrepancies among these findings likely reflect methodological differences, particularly with regard to how diabetes and cognitive impairment were defined. While most studies thoroughly assessed diabetes based on a combination of self-report, medical records, and HbA1c or fasting plasma glucose (FPG) measurements, one relied solely on medical records[53] and one explicitly excluded people with undiagnosed diabetes.[59] Furthermore, the majority of the studies measured cognitive impairment in terms of MCI,[53,55,57–60] but some instead used CIND[56] or raw cognitive test score cut-offs.[52] There were also substantial differences in the ages of the various study populations (ranging from ≥40 years to ≥70 years), as well as which covariates (e.g. age, sex, race, education, APOE ε4 genotype) were accounted for in the analyses.

Longitudinal relationship

Nine studies have addressed the longitudinal relationship between diabetes and cognitive impairment over the past 15 years.[60–68] The methods and findings of these studies are summarized in **Appendix 2**. A substantial amount of disagreement surrounds this question. To date five studies have reported a positive association between diabetes and cognitive impairment over time,[60–63,66] while four reported no association.[64,65,67,68] All studies evaluated cognitive impairment in terms of MCI.

There are several methodological discrepancies between these studies. Most importantly, the duration of follow-up ranged widely, from just 3 years[62] to 7.6 years[65] (the majority of studies fell somewhere between 4 and 5 years).[60,61,63,64,67] As for diabetes diagnosis, most studies used a combination of self-report, medical records, and laboratory tests, but the cutoff values for these tests were slightly variable (e.g. ≥6.0% vs. ≥6.5% HbA1c and ≥7.0 mmol/L vs. ≥7.8 mmol/L for FPG). Additionally, the ages of the study populations represented here were quite variable (ranging from ≥55 years[62] to ≥75 years[64]),

as were the covariates accounted for in the analysis (e.g. age, sex, race, education, APOE ε4 genotype).

Progression to dementia

Over the past 15 years, ten studies have addressed the relationship between diabetes and the progression from cognitive impairment to dementia over time.[61,64,69–76] The methods and findings of these studies are summarized in **Appendix 3**. Five studies have reported a positive association between diabetes and the progression from cognitive impairment to dementia,[64,70,72–74] while five reported no association.[61,69,71,75,76] Again, all studies evaluated cognitive impairment in terms of MCI.

Methodological discrepancies that may explain these inconsistent findings again include duration of follow-up (from 1 year[71] to 5 years[61,69,73]), diabetes diagnosis (several studies[62,69,73,74,76] relied on self-report and medication use alone without biomarker testing), and biomarker thresholds for defining diabetes (HbA1c vs. FPG, and within FPG ≥7.0 mmol/L vs. ≥7.8 mmol/L). There were additionally major differences in the demographics of the study populations and the covariates accounted for in the analyses (e.g. age, sex, race, education, APOE ε4 genotype).

IV. Prediabetes and Cognitive Impairment

In contrast to the literature on diabetes and cognitive impairment, very few studies have addressed prediabetes in relation to cognitive impairment and progression to dementia.

Cross-sectional relationship

No study to date has directly assessed the cross-sectional association between prediabetes and cognitive impairment. The investigation that most closely approaches this question is a 2017 Japanese population study of people ≥70 years of age.[77] The study was primarily concerned with the association between metabolic syndrome and MCI, but included sub-analyses for the individual components of metabolic syndrome, one of which is impaired glucose tolerance (IGT, e.g. either prediabetes or diabetes). IGT was positively associated with non-amnestic forms of MCI in both men and women (OR: 1.62, 95% CI: 1.19-2.22; OR: 1.32, 95% CI: 1.02-1.71), but not with MCI involving memory loss.[77] Furthermore, a small 2019 cohort study across several western European countries also examined IGT as sub-analyses of the various components of metabolic syndrome.[78] The study found no association between IGT and either MCI or CIND, though it is worth noting that the generalizability of this study is limited given its small size (n=202) and the fact that the study population encompassed only people undergoing elective surgery.

Longitudinal relationship

Of two longitudinal studies to examine the relationship between prediabetes and the development of

cognitive impairment – a 2010 Swedish population study (Xu et al. 2010)[64] and a 2004 population study across the United States and Canada (Yaffe et al. 2004)[67] – both found no association.

Progression to dementia

To our knowledge, Xu et al. 2010 is the only study to date that has investigated the longitudinal relationship between prediabetes and progression from cognitive impairment to dementia. Using Swedish population data from the Kungsholmen Project, the study found a strong association between prediabetes and the development of both dementia (HR=5.0, 95% CI: 2.3-10.1) and Alzheimer's disease (HR=5.7, 95% CI: 2.4-13.5) in people with baseline MCI.[64] Prediabetes was defined as random blood glucose level of 7.8-11.0 mmol/L in diabetes-free participants, in contrast to more commonly-used HbA1c or FPG thresholds. More studies are needed to conclusively determine whether this relationship between prediabetes and progression to dementia holds in other populations and with other prediabetes diagnoses.

V. Mechanisms

The mechanisms underpinning the association between diabetes and cognitive impairment have not yet been clearly delineated. Two non-mutually-exclusive candidate mechanisms include hyperglycemia and inflammation.

The chronic hyperglycemia that characterizes diabetes can lead to progressive structural and functional abnormalities in the brain. Evidence suggests that the toxic effects of hyperglycemia are mediated through many pathways, including disturbances of intracellular second messenger pathways, increased formation of advanced glycation end products (AGEs), increased glucose shunting through the polyol and hexosamine pathways, overproduction of reactive oxygen species, and altered glycation of proteins.[79] This can have damaging effects on the brain via (i) direct degradation of the myelin sheath, leading to signal processing dysfunction and neuron death, or (ii) by inducing microvascular and macrovascular changes that impair neural function indirectly.[79,80] In this way, hyperglycemia is thought contribute to widespread "micro-infarcts" in the brain that can lead to brain atrophy over time. In turn, this may lead to cognitive impairment and dementia, or lower the threshold for these to occur in response to other insults.[79]

The systemic inflammation that is associated with diabetes may also contribute to cognitive impairment and dementia.[81] In animal studies overproduction of inflammatory cytokines is associated with neurodegeneration, while in humans inflammatory markers are elevated in the brains of people with Alzheimer's disease.[81] Furthermore, epidemiological studies point to an association between inflammatory markers like C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen and elevated risk of cognitive decline and dementia.[81] Turning to pathophysiology, there are several pathways

through which the peripheral inflammatory mediators that characterize diabetes could reach the brain, including activation of cerebral endothelial cells or direct transport across the blood-brain-barrier.[81]

VI. Knowledge Gaps

Within this body of literature, several knowledge gaps remain:

First, the relationship between diabetes and cognitive impairment is not well-understood, especially in the context of CIND. Previous observational studies investigating the cross-sectional and longitudinal associations between diabetes and cognitive impairment have primarily focused on MCI (**Appendices 1-3**) and not CIND, which is more suitable for observational studies.[38]

Additionally, prediabetes has been insufficiently explored. No previous studies have investigated the cross-sectional association between prediabetes and cognitive impairment, and uncertainty remains regarding whether prediabetes impacts the incidence of cognitive impairment or its progression to dementia.

Furthermore, it is unclear whether (pre)diabetes acts alone to impact risk of cognitive impairment and dementia, or within a cluster of wider vascular disorders. Given the strong overlap between diabetes and other cardiovascular conditions and the symbiotic relationship between the brain and the heart, it is plausible that additional vascular diseases (i.e. heart disease) could exacerbate the effect of diabetes on cognitive aging.

Finally, the mechanisms underlying the impact of diabetes on cognitive impairment are poorly understood, although evidence points to diabetes-associated hyperglycemia and inflammation as two possible candidates.

Research Hypothesis

This thesis tests the hypothesis that (pre)diabetes adversely impacts cognitive function, increasing the risk of CIND and its progression to dementia over time. Vascular conditions, such as heart disease, could exacerbate diabetes' impact on cognitive impairment. Furthermore, the mechanisms by which diabetes impacts cognitive function could relate to hyperglycemia and inflammation.

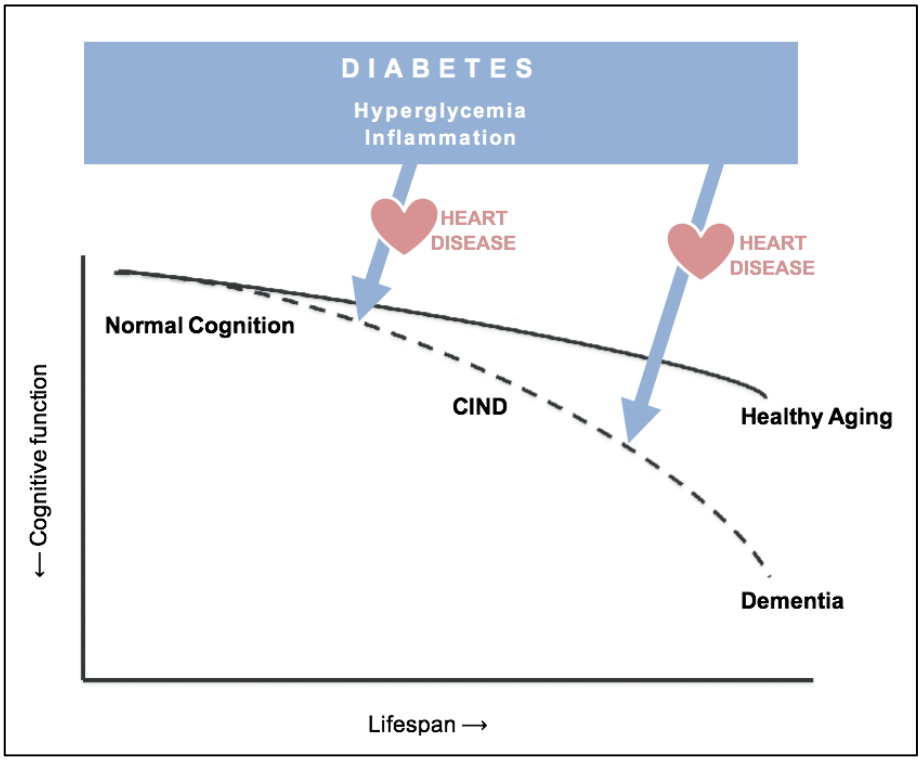

Figure 1. Schematic representation of the research hypothesis

Study Aims

The overall aim of this thesis is to investigate the impact of prediabetes and diabetes on cognitive impairment, exploring factors that exacerbate this relationship and possible underlying mechanisms.

Specifically, the following three aims were addressed:

- To investigate the associations between prediabetes, diabetes, and the development of CIND;
- To examine the extent to which prediabetes and diabetes accelerate the progression of CIND to dementia;
- To assess the role of heart disease, hyperglycemia, and inflammation in the associations between (pre)diabetes and CIND and its progression to dementia.

Methods

This study is based on baseline and 3-, 6-, 9-, and 12-year follow-up data from the ongoing population-based Swedish National Study on Aging and Care-Kungsholmen (SNAC-K).[82]

Study population

The SNAC-K population is comprised of a random sample of individuals aged ≥60 years living at home or in institutions in the Kungsholmen district, in central Stockholm, Sweden. Of 5,111 people initially invited to the study, 4,790 were alive and eligible at baseline and 3,363 (73.3%) agreed to participate in the baseline survey (March 2001 through June 2004). The sampling was stratified by eleven age-specific cohorts (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years) and participants are followed every third or sixth year (**Figure 2**). Because older age groups tend to experience more rapid changes in health and a higher study attrition rate, cohorts with individuals 78 years of age or older are followed up every three years, whereas cohorts with participants below 78 years of age are followed up every six years (until they reached the age of 78 at which point three year follow-ups were instituted). In this thesis, data were available up to 2016, for a maximum of 15 years follow-up period.

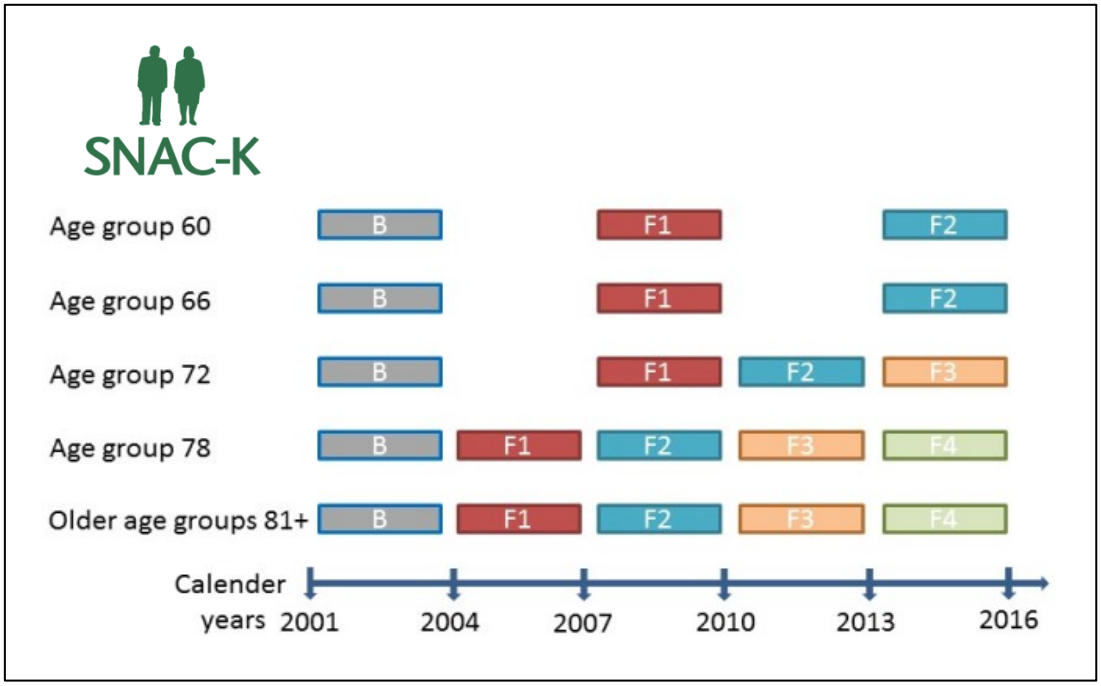

Figure 2. The Swedish National Study on Aging and Care – Kungsholmen (SNAC-K) study design. Pictured are the waves of SNAC-K assessment included in this analysis, from baseline (B) to the most recent follow-up for which data were available (F1=first, F2=second, F3=third, and F4=fourth follow-up). Modified from https://snack.se/about/study-plan

Because the present project focuses on the prodromal phase of dementia associated with prediabetes and type 2 diabetes, participants with dementia at baseline (n=250), missing data on baseline CIND status (n=464) or baseline HbA1c (n=67), neuro-psychiatric conditions (n=39 with Parkinson's disease, schizophrenia, or developmental disorders), and type 1 diabetes (n=20) were excluded. Furthermore, we also excluded individuals living in nursing homes (n=14) to avoid any possible misclassification of the outcome due to frailty and lack of functional independence. We additionally excluded one individual with prediabetes who was taking diabetes medication. Thus, this project included a total of 2,508 participants (**Figure 3**).

Based on cognitive function at baseline, the 2,508 participants were divided into to a cognitively-intact cohort (n=1,837) and a CIND cohort (n=671). The two cohorts were followed until 2016, during which incident CIND and dementia cases were detected.

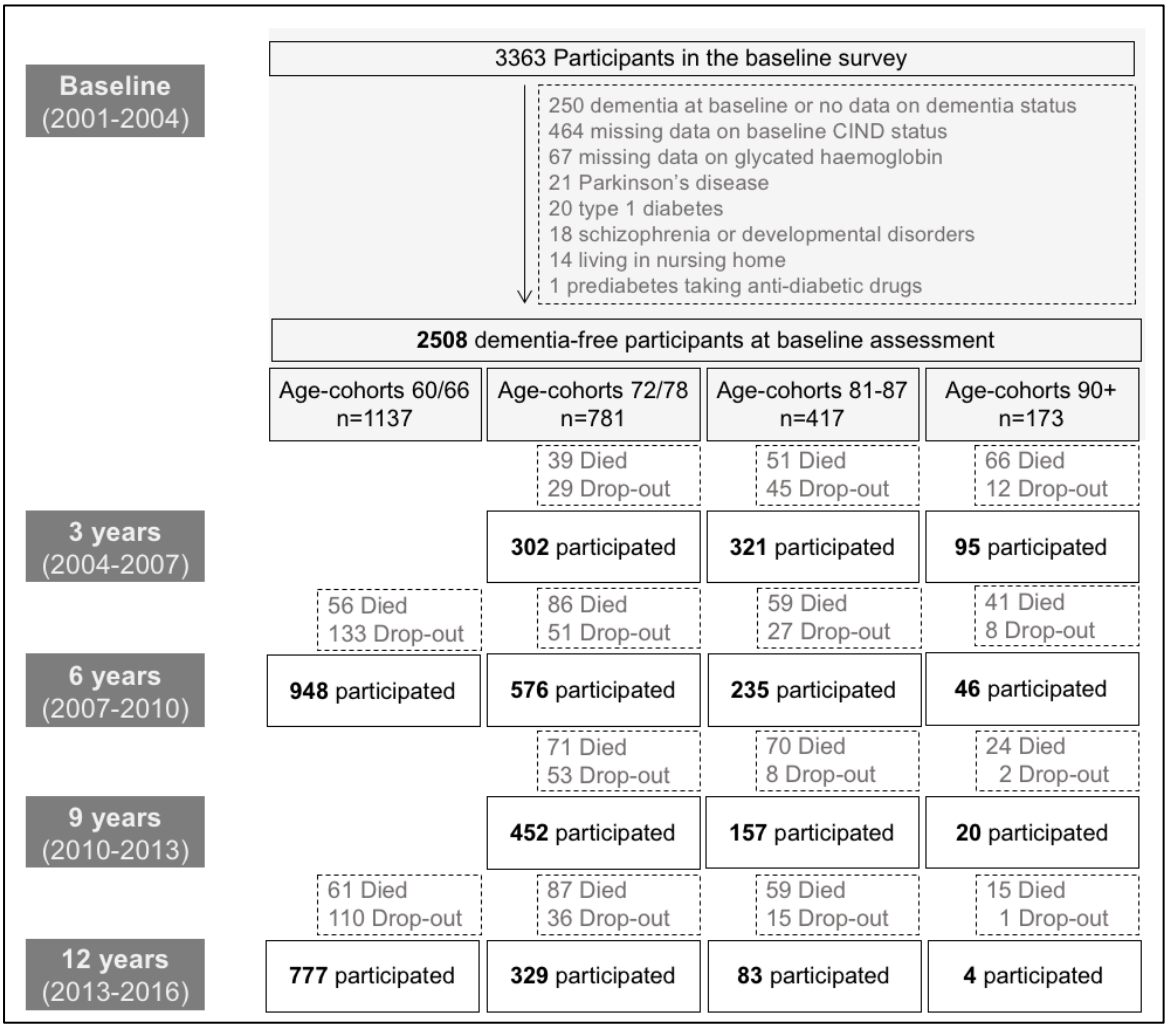

Figure 3. Flowchart of SNAC-K study population.

Ethical approval

SNAC-K was approved by the Ethical Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm, Sweden, including linkage with registries. Written informed consent was obtained from all participants, or from a proxy (i.e. family member or guardian) in the case of cognitive impairment.

Data collection

Following the standard SNAC-K protocol (available at https://www.snac-k.se/about/study-plan/), participants underwent the following examinations at baseline and during all follow-ups:

- An interview with a nurse assessing demographic data (i.e. age, sex), education and occupational history, current and past socio-economic status, living arrangement, lifestyle habits (i.e. smoking, alcohol consumption), physical functioning (i.e. ability to manage activities of daily living, motility and strength, sensory functions), and history of care received in medical and social facilities.
- A self-administered form assessing the details of the individual's social network, past and present leisure activities, nutritional habits, health-related quality of life (Short Form 12 Health Survey), life satisfaction (Neugarten Life Satisfaction Index), well-being (PANAS), and self-perceived health (Ware's Health Perceptions Questionnaire).
- A clinical examination by physicians encompassing past clinical history, family history, geriatric and neurological examinations;
- A neuropsychological assessment, in which standardized cognitive tests were administered by a trained psychologist to assess cognitive function;
- Peripheral blood sample were collected from each participant for standard laboratory tests to evaluate biochemical markers.

Assessment of diabetes and prediabetes

HbA1c was measured from peripheral blood samples with Swedish Mono S filament high-performance liquid chromatography, and 1.1% was added to the measured HbA1c values to equate them with international standards.[83]

Diabetes was identified at baseline by combining information from multiple sources: medical examination, use of anti-hyperglycemic drugs, diagnoses from the Swedish National Patient Register and the Swedish Cause of Death Registry, or HbA1c measurements ≥6.5%. In diabetes-free participants, prediabetes was defined as HbA1c of ≥5.7% to 6.4%.[84]

Participants with diabetes were classified as well-controlled (HbA1c <7.5%) or poorly-controlled (HbA1c ≥7.5%) according to recommended glycemic targets for older adults.[12]

Assessment of cognitive impairment and dementia

At baseline and at each wave of follow-up, CIND was defined as the presence of objective cognitive impairment in any domain, absent overt dementia.[36]

The neuropsychological assessment included a battery of 10 cognitive tests addressing five major cognitive domains: episodic memory (free recall),[85] perceptual speed (digit cancellation, pattern comparison),[86,87] executive function (Trial Making Test B-number of correct items),[30] visuospatial abilities (mental rotation task),[30] and verbal fluency (category and letter fluency).[30] At each wave of assessment, raw scores from the individual cognitive tests were standardized into Z-scores, using baseline means and standard deviations (SDs). The five cognitive domains were created using individual test Z-scores or by averaging the Z-scores of multiple tests. The division was made a priori, according to the standard neuropsychological practice and cognitive theory.[30]

Cognitive Impairment-no dementia (CIND) was identified as having no dementia and a score ≤1.5 SDs below age group-specific means on at least one cognitive domain of standardized cognitive tests.[36] Dementia was defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) revised criteria through a validated three-step procedure. Two examining physicians independently made preliminary diagnoses of dementia based on the participant's physical, neurological, and cognitive status (steps 1 and 2). In the case of discrepancy between the two diagnoses, a senior neurologist was consulted to reach a final diagnosis (step 3).[88] For participants who died during follow-up, the diagnosis of dementia was extracted from medical records or the death certificate, if available.

Assessment of covariates

Educational attainment was categorized into elementary, high school, and university, based on self-report. Information on physical activity was based on the participants' self-reported exercise habits and dichotomized as inactive and active (including moderate and vigorous exercise).[88] Body mass index (BMI) was calculated as the ratio of weight to squared height (kg/m^2) and grouped into the standard clinical categories: underweight (<20), normal weight (≥20-25), overweight (≥25-30), and obese (≥30). Smoking status was dichotomized as nonsmoking (participants who had never smoked) and current/ever smoking (including former and current smokers). Alcohol consumption was dichotomized as non-drinking (including non-drinkers and those who drink only occasionally) and drinking (including light-to-moderate and heavy drinkers).

Chronic medical conditions were ascertained based on physicians' examination, medical history, medication use, lab tests, and linkage with the Swedish National Patient Register (NPR), which covers inpatient care from 1987 and outpatient care since 2001.[89] Codes from the International Classification of Disease, tenth revision (ICD-10) were used to identify medical conditions including cerebrovascular diseases. Depression was diagnosed according to DSM-IV revised criteria.[90] Arterial blood pressure was measured twice at a five minute interval on the left arm in a sitting position; hypertension was identified if blood pressure exceeded 140/90 mmHg. APOE allelic status was assessed using a microsequencing method (AffiGen APOE, Sangtec Medical) based on a polymerase chain reaction with biotinylated primers. The APOE genotype was dichotomized into carriers of at least one ε4 allele versus non-carriers.

As for major covariates, heart diseases (atrial fibrillation, bradycardia, cardiac valve dysfunction, heart failure, ischemia, and peripheral vascular disease) were identified using ICD-10 codes. CRP was measured using a turbidimetric method (DXC800, Beckman Coulter). CRP was divided into three levels based on its distribution: normal (0-5 mg/L, lab reference value), high (6-20 mg/L), and very high (>20 mg/L).

Statistical analyses

Baseline characteristics of the study participants by cognitive status (cognitively-intact and CIND) and diabetes status (diabetes-free, prediabetes, and diabetes) were assessed using chi-square (χ^2) tests or one-way ANOVA, followed by pairwise mean comparisons with Bonferroni correction.

Multivariable logistic regressions were used to estimate the Odds Ratios (ORs) with 95% confidence intervals (CI) of having baseline CIND according to diabetes status.

We assessed two longitudinal outcomes in separate analyses: the development of CIND (in the cohort that was cognitively-intact at baseline) and the progression to dementia (in the cohort that had CIND at baseline).

In the cognitively-intact cohort, incidence rates (IRs) and 95% CIs of CIND per 1,000 person-years (in people with diabetes, prediabetes, and who were diabetes-free) were calculated as the number of events during the follow-up period divided by person-years of follow-up. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs of developing CIND for participants with baseline diabetes or prediabetes, in comparison to those who were diabetes-free. Follow-up time was calculated as the time from study entry until CIND diagnosis, death, or last examination. The proportional hazard assumption was tested for all predictors and covariates in the model, using the Schoenfeld residuals regressed against follow-up time. Violations of proportionality

were observed for age ($p<0.001$) and heart disease ($p=0.005$), so the model was modified to stratify by these factors.

The same procedure for calculating IRs and HRs was repeated for the CIND cohort, this time using dementia as the outcome. Follow-up time was calculated as the time from study entry until dementia diagnosis, death, or last examination. In testing the proportional hazard assumption for the Cox proportional hazards regression model, no violations of proportionality were observed.

Because cardiovascular disease is a common comorbidity of diabetes and a risk factor for cognitive impairment and dementia,[14,15] interactions between diabetes status and heart diseases were tested separately in the two cohorts (cognitively intact and CIND). First, we incorporated the two disorders (diabetes and heart disease) and their cross-product term in the same Cox regression model (multiplicative interaction). Next, we estimated the relative excess risk due to interaction (RERI) for the joint effect of diabetes and heart disease (additive interaction). Finally, to assess the joint association of diabetes and heart disease (effect modification) to predict CIND or the progression to dementia, we created an indicator variable that combined diabetes status (no vs. yes) with heart disease status (no vs. yes), effectively dividing the participants into four groups: (i) those who were diabetes-free and heart disease-free ("no disease"); (ii) those who had diabetes but no heart disease ("diabetes only"); (iii) those who had heart disease but no diabetes ("heart disease only"); and (iv) those who had both diabetes and heart disease ("diabetes and heart disease").

We additionally tested interactions between diabetes status and CRP levels in the two cohorts, given the role of systemic inflammation in the pathogenesis of both diabetes and cognitive aging.[81] We incorporated the diabetes, elevated (i.e. "high" or "very high") CRP levels, and their cross-product term in the same Cox regression model (multiplicative interaction). Furthermore, we estimated the RERI for the joint effect of CRP levels and combined diabetes and heart disease status (additive interaction).

To examine the role of hyperglycemia in relation to CIND and progression to dementia, separate logistic and Cox regression models were repeated according to the glycemic status (diabetes-free [reference], well-controlled diabetes, and poorly-controlled diabetes).

Age, sex, education, physical activity, BMI, heart disease, cerebrovascular disease, hypertension, and *APOE* ε4 status were considered as possible confounders and accounted for in data analysis.

All reported *P* values were two-sided, and *P* values <0.05 were considered statistically significant. All statistical analyses were performed using Stata SE 15.0 (StataCorp LP, College Station, Texas, USA).

Results

Baseline characteristics of the two study cohorts

Overall, of the 2,508 participants at baseline, 1,837 (73%) were cognitively-intact, 671 (27%) had CIND, 217 (9%) had diabetes, and 853 (34%) had prediabetes.

Tables 1 and **2** show the baseline characteristics in the cognitively-intact and CIND cohorts by diabetes status. In the cognitively-intact cohort, 133 (7%) participants had diabetes and 615 (34%) had prediabetes. Participants with diabetes or prediabetes were more likely to be older, to have lower levels of education, to currently drink less alcohol, and be less physically active than participants without diabetes. Moreover, they were more likely to have overweight or obesity, hypertension, heart disease, and elevated CRP levels (**Table 1**). In the CIND cohort, 84 (13%) participants had diabetes and 238 (36%) had prediabetes. Participants with diabetes were more likely to be older, to have higher BMI, more heart diseases and elevated CRP levels (**Table 2**).

We additionally compared the two cohorts (**Table 3**). Overall, the cognitively-intact cohort had a better health than the CIND cohort at baseline. In addition, among participants with diabetes, 31 (23%) in the cognitively-intact cohort and 28 (33%) in the CIND cohort had poor glycemic control.

Table 1. Baseline characteristics of the cognitively-intact cohort by diabetes status (n=1,837)

Characteristics	Diabetes-Free n=1,089	Prediabetes n=615	Diabetes n=133	*p*
Age, years	69.8 ± 9.1	72.9 ± 9.7*	72.4 ± 9.2*	<0.001
60 to <72	614 (56.4)	261 (42.4)	54 (40.6)	
72 to <81	300 (27.6)	201 (32.7)	50 (37.6)	<0.001
81 to <90	142 (13.0)	121 (19.7)	24 (18.1)	
90+	33 (3.0)	32 (5.2)	5 (3.8)	
Female	656 (60.2)	388 (63.1)	57 (42.9)	<0.001
Education				
Elementary	93 (8.5)	81 (13.2)	18 (13.5)	
High school	503 (46.2)	295 (48.0)	72 (54.1)	0.001
University	493 (45.3)	239 (38.9)	43 (32.3)	
Current/ever smokers	595 (54.8)	350 (57.2)	74 (56.5)	0.635
Current alcohol drinkers	867 (79.8)	425 (69.1)	89 (67.4)	<0.001
Physically active	888 (81.5)	459 (74.6)	88 (66.2)	<0.001
BMI, kg/m^2	25.5 ± 3.7	26.2 ± 4.1*	27.8 ± 3.8*	<0.001
Underweight (<20)	48 (4.4)	24 (3.9)	-	
Normal (20–25)	480 (44.1)	228 (37.1)	34 (25.6)	<0.001
Overweight (25–30)	450 (41.3)	263 (42.8)	59 (44.4)	
Obese (≥30)	111 (10.2)	100 (16.3)	40 (30.1)	
HbA1c, %	5.3 ± 0.22	5.9 ± 0.18*	7.1 ± 1.3*	<0.001
Heart disease	172 (15.8)	142 (23.1)	51 (38.4)	<0.001
Cerebrovascular diseases	43 (4.0)	38 (6.2)	7 (5.3)	0.113
Hypertension	730 (67.0)	417 (67.8)	111 (83.5)	0.001
Depression	38 (3.5)	22 (3.6)	4 (3.0)	0.947
CRP, mg/L	5.8 ± 3.8	6.5 ± 6.3*	6.7 ± 5.5	0.008
Normal (0-5)	909 (83.5)	488 (79.4)	95 (71.4)	
High (6-20)	153 (14.1)	103 (16.8)	31 (23.3)	0.006
Very high (>20)	27 (2.5)	24 (3.9)	7 (5.3)	
APOE ε4	310 (29.5)	169 (28.8)	31 (24.4)	0.486

Data are presented as means ± standard deviations or number (proportion %).

Missing data: Smoking=9, Alcohol=3, HbA1c=2, Depression=4, CRP=28, *APOE* ε4=74

*Pairwise means comparison using the Bonferroni correction: p<0.05 (reference group=baseline participants who were cognitively intact)

Table 2. Baseline characteristics of the CIND cohort by diabetes status (n=671)

Characteristics	Diabetes-Free n=349	Prediabetes n=238	Diabetes n=84	*p*
Age, years	74.3 ± 10.4	77.5 ± 10.6 *	75.6 ± 9.1	0.002
60 to <72	128 (36.7)	58 (24.4)	22 (26.2)	
72 to <81	116 (33.2)	79 (33.2)	35 (41.7)	0.013
81 to <90	58 (16.6)	55 (23.1)	17 (20.2)	
90+	47 (13.5)	46 (19.3)	10 (11.9)	
Female	236 (67.6)	174 (73.1)	39 (46.4)	<0.001
Education				
Elementary	74 (21.2)	62 (26.1)	23 (27.4)	
High school	188 (53.9)	132 (55.5)	40 (47.6)	0.240
University	87 (24.9)	44 (18.5)	21 (25.0)	
Current/ever smokers	171 (49.4)	129 (54.4)	50 (60.2)	0.160
Current alcohol drinkers	206 (59.4)	117 (49.6)	37 (44.6)	0.012
Physically active	230 (65.9)	151 (63.5)	49 (58.3)	0.417
BMI, kg/m^2	24.9 ± 3.8	25.5 ± 4.1	27.3 ± 5.5*	<0.001
Underweight (<20)	25 (7.2)	17 (7.1)	7 (8.3)	
Normal (20–25)	174 (49.9)	107 (45.0)	23 (27.4)	<0.001
Overweight (25–30)	121 (34.7)	83 (34.9)	31 (36.9)	
Obese (≥30)	29 (8.3)	31 (13.0)	23 (27.4)	
HbA1c, %	5.3 ± 0.24	5.9 ± 0.20*	7.2 ± 1.4*	<0.001
Heart disease	85 (24.4)	91 (38.3)	49 (58.3)	<0.001
Cerebrovascular diseases	27 (7.7)	22 (9.2)	10 (11.9)	0.458
Hypertension	253 (72.5)	186 (78.2)	59 (70.2)	0.206
Depression	28 (8.1)	15 (6.3)	8 (9.6)	0.556
CRP, mg/L	6.8 ± 9.1	6.1 ± 3.4	7.2 ± 5.1	0.356
Normal (0-5)	278 (79.7)	178 (74.8)	54 (64.3)	
High (6-20)	55 (15.8)	54 (22.7)	22 (26.2)	0.005
Very high (>20)	16 (4.6)	6 (2.5)	8 (9.5)	
APOE ε4	100 (31.6)	68 (30.2)	18 (23.1)	0.342

Data are presented as means ± standard deviations or number (proportion %).

Missing data: Smoking=5, Alcohol=5, HbA1c=3, Depression=4, CRP=17, *APOE* ε4=51

*Pairwise means comparison using the Bonferroni correction: p<0.05 (reference group=baseline participants who were cognitively intact)

Table 3. Baseline characteristics of cognitively-intact and CIND cohorts (n=2,508)

Characteristics	Intact n=1,837	CIND n=671	*p*
Age, years	71.0 ± 9.5	75.6 ± 10.4 *	<0.001
60 to <72	929 (50.6)	208 (31.0)	
72 to <81	551 (30.0)	230 (34.3)	<0.001
81 to <90	287 (15.6)	130 (19.4)	
90+	70 (3.8)	103 (15.4)	
Female	1101 (59.9)	449 (66.9)	0.001
Education			
Elementary	192 (10.5)	159 (23.7)	<0.001
High school	870 (47.4)	360 (53.7)	
University	775 (42.2)	152 (22.7)	
Current/ever smokers	1019 (55.7)	350 (52.6)	0.156
Current alcohol drinkers	1381 (75.3)	360 (54.1)	<0.001
Physically active	1435 (78.1)	430 (64.1)	<0.001
BMI, kg/m^2	25.9 ± 3.9	25.4 ± 4.2*	0.01
Underweight (<20)	72 (3.9)	49 (7.3)	<0.001
Normal (20–25)	742 (40.4)	304 (45.3)	
Overweight (25–30)	772 (42.0)	235 (35.0)	
Obese (≥30)	251 (13.7)	83 (12.4)	
HbA1c, %	5.6 ± 0.63	5.8 ± 0.80*	<0.001
Diabetes status			
Diabetes-free	1089 (59.3)	349 (52.0)	<0.001
Prediabetes	615 (33.5)	238 (35.5)	
Diabetes	133 (7.2)	84 (12.5)	
Well-controlled (HbA1c <7.5%)	102 (76.7)	56 (66.7)	<0.001
Poorly-controlled (HbA1c ≥7.5%)	31 (23.3)	28 (33.3)	
Heart disease	365 (19.9)	225 (33.5)	<0.001
Cerebrovascular diseases	88 (4.8)	59 (8.8)	<0.001
Hypertension	1258 (68.5)	498 (74.2)	0.006
Depression	64 (3.5)	51 (7.7)	<0.001
CRP, mg/L	6.1 ± 4.9	6.6 ± 7.1	0.065
Normal (0-5)	1492 (81.2)	510 (76.0)	0.014
High (6-20)	287 (15.6)	131 (19.5)	
Very high (>20)	58 (3.2)	30 (4.5)	
APOE ε4	510 (28.9)	186 (30.0)	0.614

Data are presented as means ± standard deviations or number (proportion %).

Missing data: Smoking=14, Alcohol=8, HbA1c=5, Depression=8, CRP=45, *APOE* ε4=125

*Pairwise means comparison using the Bonferroni correction: p<0.05 (reference group=baseline participants who were cognitively intact)

Cross-sectional associations between (pre)diabetes and cognitive impairment

Multi-adjusted logistic regression models showed that individuals with diabetes were 72% more likely to have CIND at baseline compared to those who are diabetes-free (OR=1.72, 95% CI: 1.23-2.41) (**Figure 4**). This relationship was stronger for poorly-controlled diabetes (HbA1c ≥7.5%), which was associated with three-times greater likelihood of CIND (OR=2.7, 95% CI: 1.45-4.93).

Such an association was not observed for prediabetes (OR=1.07, 95% CI: 0.86-1.32).

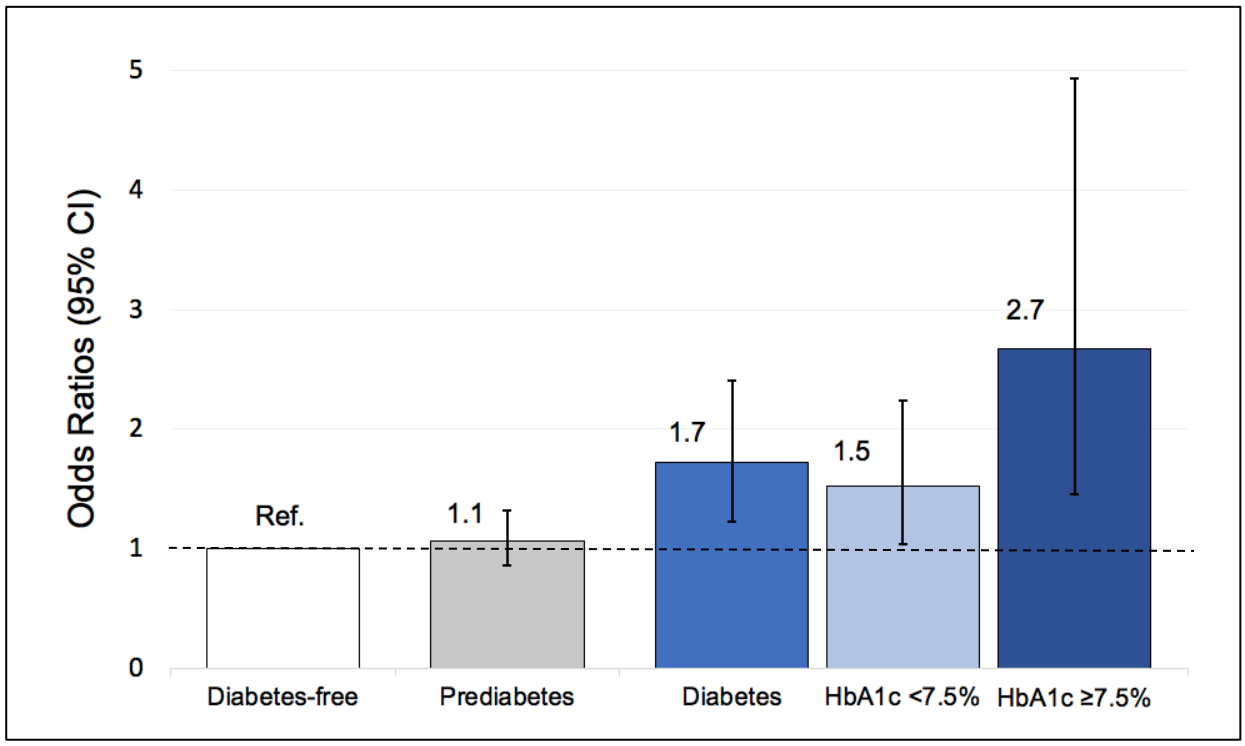

Figure 4. Logistic regressions' odds ratios (ORs) reflecting the probability of baseline CIND by diabetes status. Model adjusted for baseline age, sex, education, physical activity, BMI class, heart disease, cerebrovascular disease, hypertension, and *APOE* ε4.

Diabetes status, incident CIND, and progression to dementia

During follow-up (mean 9.2 ± 3.0 years [range=2.2-15.5 years]), 544 (30%) individuals in the cognitively-intact cohort developed CIND. In the CIND cohort, 132 (20%) individuals progressed to dementia during follow-up (mean 7.7 ± 4.0 years [range=0.2-15.2 years]). **Table 4** describes the incident rates of CIND and dementia in the cognitively-intact and CIND cohorts, respectively. For both development of CIND and progression to dementia, incidence rates were highest for participants with diabetes, particularly if they had poor glycemic control (HbA1c ≥7.5%) (**Table 4**).

Table 4. Incidence rates (IR) per 1000 person-years with 95% CI of CIND and dementia by diabetes and glycemic status.

	Incident CIND		Progression from CIND to Dementia	
	No. events/ person-year	IR (95% CI)	No. events/ person-year	IR (95% CI)
Diabetes-free	307 / 8,691	35.3 (31.6–39.5)	70 / 2,724	25.7 (20.3–32.5)
Prediabetes	191 / 4,397	43.4 (37.7–50.1)	43 / 1,691	25.4 (18.7–34.3)
Diabetes	46 / 873	52.7 (39.5–70.3)	19 / 517	36.7 (23.4–57.6)
HbA1c <7.5%	32 / 652	49.1 (34.7–69.4)	11 / 381	28.8 (16.0–52.1)
HbA1c ≥7.5%	14 / 221	63.3 (37.5–106.9)	8 / 136	59.0 (29.5–117.9)
Total	544 / 13,961	39.0 (35.8–42.4)	132 / 4,932	26.8 (22.6–31.7)

A multi-adjusted Cox proportional hazards model showed that diabetes was borderline associated with increased risk of CIND (HR 1.4, 95% CI:0.98-1.88, p=0.068) in the cognitively intact cohort (**Table 5**). This was primarily driven by participants with poorly-controlled diabetes (HbA1c ≥7.5%) who showed 2-times higher risk of developing CIND than those who were diabetes-free (HR 2.0, 95% CI:1.11-3.48). Furthermore, in the CIND cohort, poorly-controlled diabetes was also associated with a 3-times higher risk of dementia progression (HR 3.3, 95% CI: 1.29-8.33).

No associations between prediabetes and CIND were detected in either cohort (**Table 5**).

Table 5. Hazard ratios (HR) with 95% CI of incident CIND and progression to dementia by diabetes and glycemic status.

	Incident CIND			Progression from CIND to Dementia		
		Basic-adjusted	*Multi-adjusted*		*Basic-adjusted*	*Multi-adjusted*
	n	HR (95% CI) *	HR (95% CI) †	n	HR (95% CI) *	HR (95% CI) †
Diabetes-free	1,089	Reference	Reference	349	Reference	Reference
Prediabetes	615	1.1 (0.96–1.38)	1.1 (0.94–1.36)	238	0.81 (0.55–1.18)	0.78 (0.52–1.17)
Diabetes	133	1.4 (0.99–1.86) ǂ	1.4 (0.98–1.88) ǂ	84	1.4 (0.82–2.31)	1.2 (0.68–2.07)
HbA1c <7.5%	78	1.2 (0.86–1.79)	1.2 (0.86–1.79)	43	1.0 (0.54–1.94)	0.87 (0.44–1.69)
HbA1c ≥7.5%	55	1.7 (1.00–2.94) ǂ	**2.0 (1.11–3.48)**	41	**2.8 (1.28–5.91)**	**3.3 (1.29–8.33)**

* Basic-adjusted for baseline age, sex, and education.

† Multi-adjusted for baseline age, sex, education, vascular risk factors (i.e. physical activity and BMI), heart disease, cerebrovascular disease, hypertension, and *APOE* ε4.

ǂ p-value <0.07 indicating borderline statistical significance.

The role of cardiovascular diseases

We tested whether diabetes and poorly-controlled diabetes interacted synergistically with cardiovascular diseases in exacerbating the development of CIND and its progression to dementia.

In the cognitively-intact cohort, there was no indication of a multiplicative interaction between diabetes and heart disease (p=0.145). Additionally, there was no additive interaction (RERI=0.19, 95% CI: -0.33-0.70, p=0.497). Next, we further examined the joint association of diabetes and heart diseases in predicting cognitive impairment combining diabetes (no vs. yes) and heart disease (no vs. yes) in an indicator variable (**Figure 5**). Neither diabetes nor heart disease alone were associated with an increased risk of CIND. However, comorbid diabetes and heart disease were associated with more than double the risk of CIND (HR 2.2, 95% CI: 1.39-3.48, p=0.001) compared to disease-free participants. Poor glycemic control strengthened this association slightly (HR for the joint association between poorly-controlled diabetes [HbA1c≥7.5%] and heart disease = 2.3, 95% CI:1.09-4.64).

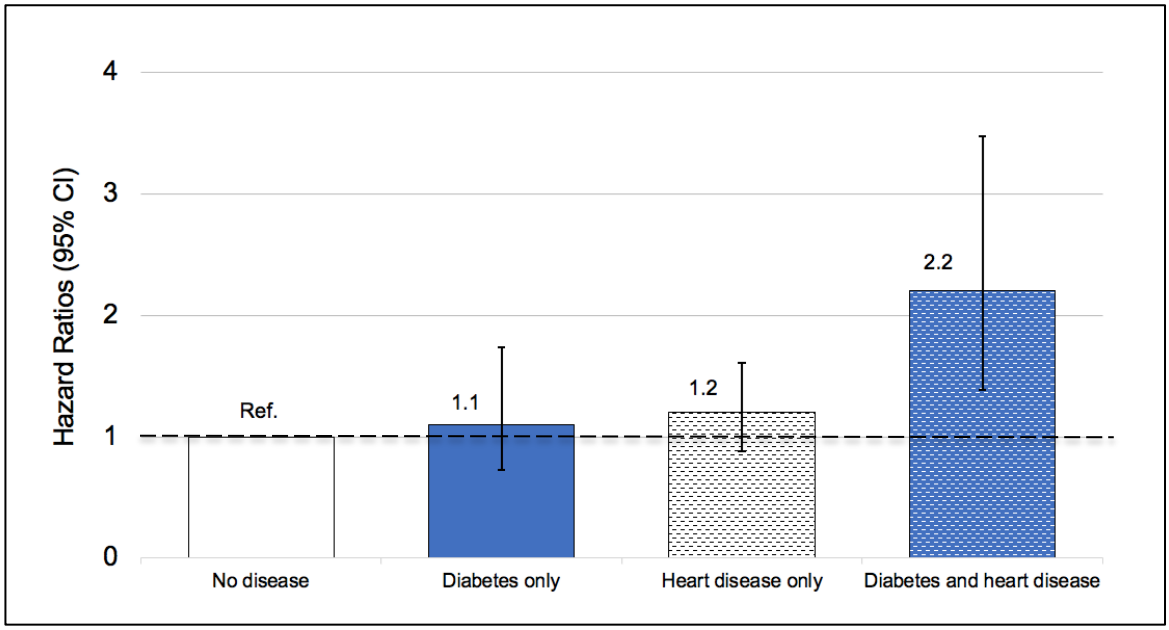

Figure 5. Hazard ratios (HRs) with 95% CI of CIND for cognitively-intact participants by diabetes and heart disease status. Model adjusted for baseline age, sex, education, physical activity, BMI class, cerebrovascular disease, hypertension, and *APOE* ε4.

In the CIND cohort, we found a statistically significant multiplicative interaction between diabetes and heart disease (p=0.040). Specifically, in participants with CIND and heart disease, the additional diagnosis of diabetes increased the risk of progressing to dementia by 2.5-fold (HR 2.5, 95% CI: 1.17-5.47). This risk rises to nearly 6-fold when diabetes is poorly-controlled (HR 5.8, 95% CI: 1.72-19.3) (**Table 6**).

Table 6. Hazard ratios (HR) with 95% CI of progression to dementia for CIND cohort participants with and without heart disease, by diabetes status.

	Heart Disease-Free		Heart Disease	
	n	HR (95% CI) †	*n*	HR (95% CI) †
Diabetes-free	264	Reference	85	Reference
Prediabetes	147	0.69 (0.42–1.14)	91	1.2 (0.58–2.3)
Diabetes	35	0.71 (0.25–1.98)	49	**2.5 (1.17–5.47)**
HbA1c <7.5%	28	0.58 (0.18–1.90)	28	1.7 (0.63–4.38)
HbA1c ≥7.5%	7	1.4 (0.18–10.0)	21	**5.8 (1.72–19.3)**

† Multi-adjusted for baseline age, sex, education, vascular risk factors (i.e. physical activity and BMI), cerebrovascular disease, hypertension, and *APOE* ε4.

The role of inflammation

To assess the role of systemic inflammation in predicting diabetes-related cognitive impairment, we further tested interactions (multiplicative and additive) between diabetes or glycemic control and CRP levels. Because of the low number of participants with very high CRP levels in the prediabetes (n=8) and diabetes (n=15) groups, we merged the high CRP and very high CRP groups into one, called "elevated CRP." In the cognitively-intact cohort, no statistically significant interactions were detected between diabetes and CRP levels. However, in the CIND cohort, we found a statistically significant multiplicative interaction between diabetes and elevated CRP levels (p=0.047). Specifically, in participants with CIND, having diabetes and elevated CRP increases the risk of progressing to dementia by over 4-fold (HR 4.1, 95% CI: 1.15-14.22). This was particularly driven by poorly-controlled diabetes (HR 13.6, 95% CI: 1.89-98) (**Table 7**).

Table 7. Hazard ratios (HR) with 95% CI of progression to dementia for CIND cohort participants with normal and elevated CRP levels, by diabetes status.

	Normal CRP		Elevated CRP	
	n	HR (95% CI) †	*n*	HR (95% CI) †
Diabetes-free	278	Reference	71	Reference
Prediabetes	178	0.67 (0.43-1.05)	60	2.0 (0.66-6.26)
Diabetes	54	0.93 (0.48-1.79)	30	**4.1 (1.15-14.22)**
HbA1c <7.5%	45	0.71 (0.33-1.52)	11	0.84 (0.12-5.85)
HbA1c ≥7.5%	9	3.1 (0.86-11.07)	19	**13.6 (1.89-98.0)**

† Multi-adjusted for baseline age, sex, education, vascular risk factors (i.e. physical activity and BMI), heart disease, cerebrovascular disease, hypertension, and *APOE* ε4.

Given the elevated risk of progression to dementia in people with diabetes and (i) heart disease and (ii) elevated CRP, we additionally tested whether CRP levels modified the joint association between diabetes and heart disease in raising the risk of dementia. No additive interactions were detected between comorbid diabetes and heart disease and CRP levels (RERI= -0.88, 95% CI:-1.89-0.13, p=0.09). Furthermore, although the directionality of the HRs suggests a greater risk of dementia for the joint association of comorbid diabetes and heart disease plus high inflammation, no statistically significant associations between comorbid diabetes and heart disease and elevated CRP levels were detected (**Table 8**).

Table 8. Hazard ratios (HR) with 95% CI of progression to dementia for CIND cohort participants with normal and elevated CRP levels, by diabetes and heart disease status.

	Normal CRP		**Elevated CRP**	
	n	HR (95% CI) †	*n*	HR (95% CI) †
No disease	219	Reference	45	Reference
Diabetes only	27	0.36 (0.10-1.27)	8	1.7 (0.10-30.0)
Heart disease only	59	1.1 (0.56-2.06)	26	1.4 (0.18-10.5)
Diabetes and heart disease	27	1.7 (0.75-3.68)	22	4.1 (0.77-21.7)

† Multi-adjusted for baseline age, sex, education, vascular risk factors (i.e. physical activity and BMI), cerebrovascular disease, hypertension, and *APOE* ε4.

Discussion

In this large-scale, population-based longitudinal study of older adults followed for up to 15 years, we found that poorly-controlled diabetes was associated with double the risk of incident CIND and triple the risk of progression from CIND to dementia. The risk of progression to dementia was further exacerbated by the presence of heart disease and elevated levels of systemic inflammation in people with diabetes, particularly those with poor glycemic control. Our findings highlight diabetes (particularly poorly-controlled diabetes) and its cardiovascular complications as ideal targets for interventions to prevent cognitive impairment and dementia – conditions for which there is currently no available pharmacological treatment.

The association of diabetes with cognitive impairment and its progression to dementia has been widely investigated in population-based studies of older adults, showing mixed findings. Five studies reported that diabetes is associated with incident cognitive impairment,[60–63,66] while four studies did not observe such an association (**Appendix 2**).[64,65,67,68] Similarly, as for diabetes' role in progression from cognitive impairment to dementia, five studies reported an association, [64,70,72–74] whereas five did not (**Appendix 3**).[61,69,71,75,76] Discrepancies in the literature could in part reflect methodological differences, particularly with regard to the assessment of diabetes (HbA1c, FPG, or oral glucose tolerance test [OGTT]), the duration of follow-up, and demographics of the study populations. Additionally, the majority of these studies did not take into account whether participants were above or below recommended thresholds for good glycemic control, omitting crucial information about the severity of diabetes within the study population.

Our study, which examines degree of glycemic control in addition to general diabetes status, adds to this body of literature and may shed some light on its inconsistencies. We found that poorly-controlled (HbA1c ≥7.5%) diabetes was associated with a greater risk of incident cognitive impairment and progression from cognitive impairment to dementia. Overall this indicates that the impact of diabetes on these adverse cognitive outcomes is exacerbated by higher levels of hyperglycemia.

At the biological level, it is hypothesized that hyperglycemia could (i) directly degrade the myelin sheath of neurons, leading to signal processing dysfunction and neuronal death, and (ii) indirectly impair neural function by inducing microvascular and macrovascular changes in the brain.[79] Together these contribute to micro-infarcts and brain atrophy, which lower the threshold for cognitive impairment and dementia to occur in response to other insults to the brain.[79] Our results highlighting the exacerbating role of poor glycemic control on the associations between diabetes and these cognitive outcomes are consistent with this theoretical framework – people with poorly-controlled diabetes could have a higher risk of adverse cognitive outcomes because excessive hyperglycemia could lower the threshold for brain damage.

Notably, in the present study we found that prediabetes – a state characterized by only slight hyperglycemia – confers no additional risk of CIND or its progression to dementia compared with normoglycemia. This finding adds further support to the idea that the degree of hyperglycemia impacts the threshold at which adverse cognitive outcomes occur. Therefore, prediabetes could represent a crucial window of opportunity for reducing the risk of cognitive impairment (and ensuing dementia) that would come with progression to diabetes.

It is plausible that interventions for diabetes prevention, aiming to restore normoglycemia, could also show benefits for cognitive impairment and dementia. Major clinical trials to prevent diabetes such as the Finnish Diabetes Prevention Study[91] and the US Diabetes Prevention Program[92] have demonstrated that intensive lifestyle modification (e.g. diet and exercise in a structured education program) can substantially and enduringly reduce the incidence of diabetes in people with prediabetes (-43% over 7 years and -27% over 15 years, respectively). Likewise, the recent Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrates that a multi-domain intervention consisting of diet, exercise, cognitive training, and vascular risk monitoring can maintain or even improve cognitive function in older adults.[93] However, to date, no studies have demonstrated the that the same multi-domain lifestyle-related intervention has simultaneous beneficial effects for both diabetes and cognitive impairment. Thus, future randomized controlled trials (RCTs) are needed to directly assess whether interventions for diabetes prevention also promote prevention of cognitive impairment and dementia.

Our findings further highlight that diabetes does not act alone to increase the risk of cognitive impairment and its progression to dementia, but as part of a cluster of wider vascular disorders including heart disease. A large body of research focuses on the morbidity and mortality that results from the combined diagnoses of diabetes and heart disease, but comparatively little has been done to understand how the intersection of these diseases affects cognitive outcomes. To our knowledge, only one longitudinal study has previously assessed the risk of dementia associated with comorbid diabetes and heart disease (among other combinations of various vascular risk factors).[94] This study reported a nearly 4-fold greater risk of "probable and possible Alzheimer's disease" dementia in individuals with comorbid diabetes and heart disease (HR 3.7, 95% CI: 1.2-11.1) in a small sample (n=246).[94]

In line with this finding, in our study heart disease acted synergistically with diabetes to exacerbate the risk of these adverse cognitive outcomes. In cognitively-intact participants, comorbid diabetes and heart disease more-than-doubled the risk of incident CIND, whereas neither diabetes nor heart disease alone had a significant impact. Furthermore, in participants with CIND, having diabetes and comorbid heart disease substantially increased the risk of dementia by 2.5-fold vs. heart disease alone (6-fold if diabetes was poorly-controlled).

The elevated risk of dementia with comorbid diabetes and heart disease is consistent with the emerging view that heart disease, like diabetes, is itself an independent risk factor for dementia. Observational studies have reported associations between dementia and specific cardiovascular conditions including coronary artery disease, MI, atrial fibrillation, valvular disease, and heart failure.[95] Emerging evidence suggests that these diseases may affect the brain through not only via large-vessel disorders (e.g. stroke, coronary atherosclerosis) but also through small vessel disease.[95,96] All heart diseases in some way reduce cerebral blood flow, which can in turn worsen the brain's vascular homeostasis, disrupt the blood-brain-barrier, and increase susceptibility to neurological insults.[95] These mechanisms would exacerbate the detrimental effects of hyperglycemia to further lower the threshold for insults to the brain. Separately, the presence of heart disease in people with diabetes may also indicate greater diabetes severity, since this complication is more likely to emerge with longer diabetes duration and the increased exposure to oxidative stress and inflammation that characterizes poorly-controlled diabetes.[97]

At the biochemical level, systemic chronic inflammation has been proposed as a key factor linking dementia with vascular disorders such as diabetes and heart disease.[18,81,98] Inflammation contributes to the insulin resistance that leads to diabetes, and is further increased by disruptions in glucose metabolism once diabetes sets in.[81,98] Over time, elevated concentrations of inflammatory mediators like CRP, IL-6, and fibrinogen can lead to cognitive impairment and dementia.[18,98] In support of this hypothetical framework, our study highlights an interaction between diabetes and inflammation such that people with diabetes and elevated CRP levels have a 4-fold increased risk of progression from cognitive impairment to dementia. This soars to a nearly 14-fold increased risk with poorly-controlled diabetes.

Strengths of this study include the longitudinal design with a long follow-up (up to 15 years), high participation rate (73% of those invited to the study), and relatively large sample size (n=2,508). Additional strengths include repeated measurements of cognitive functioning over the course of regular study visits, diagnosis of CIND through a comprehensive neuropsychological battery, and comprehensive assessment of diabetes status based on integration of data from Swedish national registries with clinical diagnoses collected by the examining physicians. Furthermore, our assessment of dementia status was corroborated by death certificates or medical records at hospital discharge in participants who died during follow-up.

However, some limitations must be acknowledged. First, selection bias may have occurred because of nonresponse over follow-up, leading to a younger and relatively healthier sample. That said, number of people who dropped out of the study was small and, if anything, this would only underestimate the reported associations between diabetes, CIND, and dementia. Additionally, the biomarker used to define (pre)diabetes in the SNAC-K study, HbA1c, has comparably low sensitivity than FPG or OGTT, widely considered the gold standards for diabetes diagnosis.[99] Thus, a proportion of diabetes

cases may not have been detected. These participants would have been misclassified as diabetes-free, leading to an underestimation of the associations presented in this thesis. Another limitation of this study is reduced statistical power when examining the impact of poorly-controlled diabetes, given the comparatively small sample size of participants (n=31 in the cognitively-intact cohort; n=28 in the CIND cohort). This would also contribute to an underestimation of the investigated associations. In addition, CRP is not an ideal measure of the chronic low-grade inflammation that is of interest in the context of diabetes, since CRP levels can be drastically altered in instances of acute inflammation such as infection.[100] Future studies using other more specific inflammatory markers (e.g. interleukins) are warranted. Finally, we cannot rule out the influence of potential residual confounding due to unmeasured environmental, geographical, or stress-related factors.

Our findings are generalizable to western populations with similar demographic characteristics as the SNAC-K population (i.e. urban and predominantly highly-educated Caucasians). With overall diabetes prevalence of 8.6%, it should be noted that our study population has markedly better metabolic health than the overall Swedish population aged ≥65 (diabetes prevalence estimated at 15.6% in 2013),[101] which is itself healthier than many other western nations – particularly the United States, where diabetes prevalence in people ≥65 is estimated at 22-33%.[102] Considering this, plus the methodological issues outlined above that may underestimate the effect size, we believe the true extent to which diabetes increases the risk of cognitive aging – and the burden of this for society – is even greater than our results suggest.

In summary, this study provides evidence of an accelerated progression of cognitive decline (i.e. incident CIND and its worsening to dementia) with poorly-controlled diabetes. The presence of heart disease or high systemic inflammation in addition to diabetes further worsens the prognosis for cognitive impairment progressing to dementia.

Future studies are needed to address synergistic interactions between mechanisms (e.g. hyperglycemic, inflammatory, or both) underlying the connection between diabetes, cognitive impairment, and dementia. Furthermore, turning toward solutions to fight the rise of diabetes-driven dementia, it is of great importance to determine whether diabetes prevention interventions also reduce the risk of cognitive impairment and dementia. Great public health significance lies in the possibility of addressing two of society's most burdensome age-related diseases together with the same interventions.

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Appendix 1—The cross-sectional relationship between diabetes and cognitive impairment

Reference	Study population	Diabetes	Cognitive impairment	Results*	Covariates†
Kotsani et al, 2018 Greece	Population-based n = 403 Aged ≥65 y	Self-report Medical records HbA1c ≥6.5%	MMSE score <26 ICDT score <10	**OR 2.0 (1.2-3.4)** **OR 1.5 (1.0 – 2.4)**	Age, sex, education, ischemic heart disease, history of stroke or MI, depression, disability, TUG, self-rated health status, self-rated memory complaint
Li et al 2018 China	Population-based n = 865 Aged ≥55 y	Medical records Medication use FPG ≥7.0 mmol/L	MCI: Petersen (2004)	OR 1.4 (0.91-2.19)	Age, sex, education, marital status, smoking, drinking, inactivity, hypertension, CHD, dyslipidemia, triglycerides, cholesterol
Chen et al, 2016 China	Clinical–based multicenter n = 3988 Aged ≥50	Medical records	MCI: MoCA score <26	**OR 1.24 (1.03–1.50)**	Age, sex, education, marital status, smoking, physical activity, dyslipidemia, BMI≥25, hypertension
Winkler et al, 2014 Germany	Population–based n = 1936 Aged 50-80	Self-report Medication use FPG ≥7.0 mmol/L no-FPG ≥11.0 mmol/L Undiagnosed diabetes was excluded	MCI: Petersen (2004) amnestic MCI non-amnestic MCI	Middle-age (50-65 yrs): **MCI: OR 2.18 (1.38–3.43)** **aMCI: OR 2.33 (1.33–4.06)** **naMCI: OR 2.00 (1.07–3.73)** Old-age (65-80 yrs): MCI: OR 1.09 (0.76–1.57) aMCI: OR 1.09 (0.69–1.71) naMCI: OR 1.10 (0.69–1.75)	Age, sex, education, smoking, BMI, CVDs, hypertension, depression

Roberts et al, 2014 USA	Population–based n = 1437 Aged 70-89	Medication use Medical records FPG >126.0 mg/dL	MCI: Petersen (2004)	**OR 2.04 (1.09–3.81)**	Age, sex, education, smoking, obesity, hypertension, dyslipidemia, APOE ε4
O´Bryant et al, 2013 USA	Two population–based: FRONTIER n = 509 Aged ≥40 TARCC n = 1098 Aged ≥50	Self-report Medication use FPG >126.0 mg/dL	MCI: Petersen (2004)	FRONTIER: **OR 1.99 (1.09–3.81)** TARCC: OR 1.13 (0.71–1.78)	Age, sex, education, obesity, hypertension, hyperlipidemia, depressive symptoms, APOE ε4
Atti et al, 2010 Italy	Population–based n = 7389 Aged ≥60	Self-report Medical records Clinical examinations	CIND: <2 SDs of the adjusted MMSE mean of dementia-free participants	**OR 1.62 (1.18–2.21)**	Age, sex, education, marital status, SES, vascular risk factors (smoking, alcohol, BMI), medical conditions
Roberts et al, 2008 USA	Population–based case–control n = 1969 Aged ≥70	Self-report Medication use Medical records FPG ≥126.0 mg/dL no-FPG ≥114.0 mg/dL	MCI: Petersen (2004) amnestic MCI non-amnestic MCI	OR 1.33 (0.98–1.81)	Age, sex, education, smoking, BMI, hypertension, stroke/TIA

* Results are reported as *Odds Ratio (95% Confidence intervals)*. Reference group included diabetes-free participants. **Bold** indicates the presence of an association.

Abbreviations: aMCI, amnestic mild cognitive impairment; APOE ε4, Apolipoprotein ε4 allele; BMI, body mass index; CIND, cognitive impairment-no dementia; CVDs, cardiovascular disease; FPG, fasting plasma glucose; no-FPG, non-fasting plasma glucose; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; naMCI, non-amnestic mild cognitive impairment; OR, odds ratio; SD, standard deviation; SES, socioeconomic status; TIA, transient ischemic attack

Appendix 2—The longitudinal relationship between (pre)diabetes and cognitive impairment

Reference	Study population	Follow-up	Diabetes	Cognitive Impairment	Results*	Covariates
Rawlings et al, 2019 USA	Clinical-based multicenter (ARIC) n = 5,099 Aged 69-88	5 years	Self-report Medication use HbA1c ≥6.5%	MCI: Petersen (2004)	**HR 1.14 (1.00-1.31)** **A1c ≥7%: HR 1.38 (1.12-1.69)** A1c <7%: HR 1.05 (0.91-1.22)	Age, race, sex, education, drinking, smoking, hypertension, APOE ε4, history of stroke, history of CHD
Ng et al, 2016 Singapore	Population–based n = 1,519 Aged ≥55	3 years	Self-report Medication use	MCI: Petersen (2004)	**HR 2.84 (1.92–4.19)**	Age, sex, education, smoking, physical, social, productive activities score, APOE ε4
Roberts et al, 2014 USA	Population–based n = 1,450 Aged ≥70	4 years	Medication use Medical records FPG ≥126.0 mg/dL	MCI: Petersen (2004) amnestic MCI non-amnestic MCI	**HR 1.42 (1.06–1.91)** **aMCI: HR 1.58 (1.12–2.25)** naMCI: HR 1.28 (0.72–2.25)	Age, sex, education, BMI≥30, moderate exercise, CVDs, hypertension, dyslipidemia, depression, statins, APOE ε4
Ganguli et al, 2013 USA	Population–based n = 1,636 Aged ≥65	4 years	Self-report HbA1c ≥6.0%	MCI: cognitive domains score <1 SD of normative mean	**HR 1.51 (1.04–2.20)**	Age, sex, education, attrition bias
Xu et al, 2010 Sweden	Population–based n = 963 Aged ≥75	4.8 years	Self-report Medication use Medical records no-FPG ≥11.0 mmol/L	MCI: Petersen (2004)	Prediabetes: HR 1.1 (0.4–2.7) Diabetes: HR 1.0 (0.4–2.8)	Age, sex, education, baseline MMSE, BMI, CVDs, survival status, APOE ε4
Panza et al, 2008 Italy	Population–based n = 1,445 Aged ≥65	7.6 years	Self-report Medication use Medical records FPG ≥ 140 mg/dL	MCI: Petersen (1999) SMC not taken into account	RR 1.1 (0.7–1.4)	Age, sex, education, smoking, total cholesterol, CVDs, hypertension

Luchsinger et al, 2007 USA	Population–based n = 918 Aged ≥65	6.1 years	Self-report Medication use	MCI: Petersen (1999) amnestic MCI non-amnestic MCI	**HR 1.4 (1.0–1.8)** **aMCI: HR 1.5 (1.0–2.2)** naMCI: HR 1.28 (0.9–1.8)	Age, sex, education, ethnicity, smoking, CVDs, hypertension, LDL-c, APOE ε4
Yaffe et al, 2004 USA, Canada	Population–based n = 4,961 women Aged >60	4 years	Self-report Medication use FPG ≥ 7.0 mmol/L	MCI: Petersen (1999)	Prediabetes: OR 1.06 (0.51–2.20) Diabetes: OR 1.78 (0.99–3.20)	Age, treatment
Solfrizzi et al, 2004 Italy	Population–based n = 1,524 Aged >65	3.5 years	Self-report Medication use Medical records FPG ≥ 7.8 mmol/L	MCI: Petersen (1999) SMC not taken into account; non-cognitive disabilities and comorbidities included	No association (not reported)	Age, sex, education, smoking, CVDs, hypertension, total cholesterol, HDL-c

* Results are reported as *Hazard Ratio (95% Confidence intervals)*. Reference group included diabetes-free participants. **Bold** indicates the presence of an association.

Abbreviations: aMCI, amnestic mild cognitive impairment; APOE ε4, Apolipoprotein ε4 allele; BMI, body mass index; CIND, cognitive impairment-no dementia; CHD, chronic heart disease; CVDs, cardiovascular disease; FPG, fasting plasma glucose; no-FPG, non-fasting plasma glucose; HbA1c, glycated hemoglobin; HR, hazard ratio; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; naMCI, non-amnestic mild cognitive impairment; OR, odds ratio; RR, relative risk; SD, standard deviation; SES, socioeconomic status; SMC, subjective memory complains

Appendix 3—The relationship between (pre)diabetes and the progression from cognitive impairment to dementia

Reference	Study population	Follow-up	Diabetes	Cognitive Impairment and Dementia	Results*	Covariates†
Rawlings et al, 2019 USA	Clinical-based multicenter (ARIC) n = 5,099 Aged 69-88	5 years	Self-report Medication use HbA1c ≥6.5%	MCI: DSM-V Dementia: DSM-V	HR 1.15 (0.90-1.47) A1c ≥ 7%: 1.38 (0.96-2.00) A1c <7%: 1.02 (0.78-1.35)	Age, race, sex, education, drinking, smoking, hypertension, APOE4, history of stroke, history of CHD
Ganguli et al, 2019 USA	Population-based n = 356 Aged ≥65	5 years	Self-report	MCI: CDR score 0.5-1 Dementia: CDR score >1	RR 1.31 (0.94-1.68)	"Adjusted for demographic characteristics"
Ng et al, 2016 Singapore	Population–based n = 2042 Aged ≥55	3 years	Self-report Medication use	MCI: Petersen (2004) Dementia: DSM-IV	**HR 2.5 (1.9–4.2)**	Age, sex, education, smoking, physical, social, productive activities score, APOE genotype
Viticchi et al, 2012 Italy	Clinical–based n = 117 Mean age 75.7	1 year	Self-report Medication use FPG >7.0 mmol/L	MCI: Petersen (2001) Dementia: DSM-IV	Dementia: OR 1.3 (0.4–4.7)	Age, sex, education, smoking, carotid plaques, hypertension, baseline cognition, cerebrovascular reactivity
Li et al, 2012 China	Clinical–based n = 257 Aged ≥60	3 years	FPG >7.0 mmol/L	MCI: Petersen (2011) Dementia: DSM-IV AD: NINCS-ADRDA	Dementia: **HR 2.4 (1.1–5.3)** AD: **HR 2.9 (1.1–7.6)**	Not specified
Li et al, 2011 China	Population–based n = 837 Aged ≥55	5 years	Medical records Medication use	MCI: Petersen (1999)	**HR 1.6 (1.0–2.6)**	Age, sex, education, occupation, ADL, depression, APOE4, baseline MMSE

Xu et al, 2010 Sweden	Population–based n = 1098 Aged ≥75	4.8 years	Self-report Medical records Medication use no-FPG ≥11.0 mmol/L	MCI: Petersen (2004) Dementia: DSM-III-R AD: NINCS-ADRDA	<u>Prediabetes</u> **Dementia: HR 5.0 (2.3–10.1)** **AD: HR 5.7 (2.4–13.5)** <u>Diabetes</u> **Dementia: HR 2.9 (1.3–6.3)** **AD: HR 2.8 (1.2–6.8)**	Age, sex, education, baseline cognition, BMI, CVDs, hypertension, survival status, APOE genotype
Velayudhan et al, 2010 UK	Population–based n = 103 Aged ≥65	4 years	Self-report Medical records Medication use	MCI: Petersen (1999) Dementia: DSM-IV	**HR 2.9 (1.1–7.3)**	Age, sex, education, baseline cognition, VRFs (smoking, alcohol, BMI), CVDs, depression, APOE4, diabetes duration
Artero et al, 2008 France	Population–based n = 2882 Aged ≥65	4 years	Self-report	MCI: Petersen (1999) Dementia: DSM-IV	Not significant (not reported)	Not reported
Ravaglia et al, 2006 Italy	Clinical–based n = 165 Aged ≥60	2.8 years	Self-report Medical records	MCI: Petersen (2004) Dementia: DSM-IV	HR 0.8 (0.3–2.1)	Age, sex, education

* Results are reported as *Hazard Ratio (95% Confidence intervals)*. Reference group included diabetes-free participants. **Bold** indicates the presence of an association.
Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; aMCI, amnestic mild cognitive impairment; APOE ε4, Apolipoprotein ε4 allele; BMI, body mass index; CIND, cognitive impairment-no dementia; CHD, chronic heart disease; CVDs, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; FPG, fasting plasma glucose; no-FPG, non-fasting plasma glucose; HbA1C, glycated hemoglobin; HR, hazard ratio; LDL-c, low density lipoprotein cholesterol; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; naMCI, non-amnestic mild cognitive impairment; NINCS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke & Alzheimer's Disease and Related Disorders Association; OR, odds ratio; RR, relative risk; SD, standard deviation; SES, socioeconomic status; SMC, subjective memory complains; TIA, transient ischemic attack; VRFs, vascular risk factors